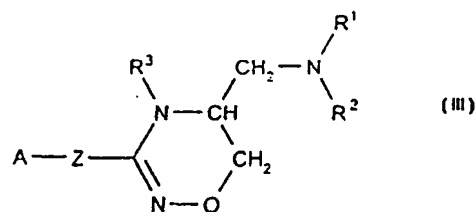
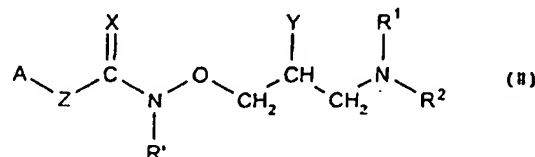
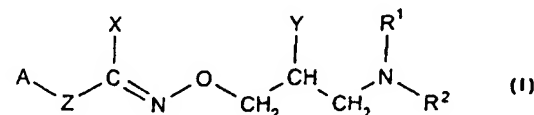




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>(21) International Application Number: PCT/HU97/00044</p> <p>(22) International Filing Date: 6 August 1997 (06.08.97)</p> <p>(30) Priority Data:  P 96 02204      9 August 1996 (09.08.96)      HU  P 97 01349      4 August 1997 (04.08.97)      HU</p> <p>(71) Applicant (for all designated States except US): BIOREX KUTATÓ ÉS FEJLESZTŐ RT. [HU/HU]; Szabadságpuszta, H-8200 Veszprém (HU).</p> <p>(72) Inventors; and  (75) Inventors/Applicants (for US only): JEDNÁKOVITS, Andrea [HU/HU]; Lévai u. 3, H-2000 Szentendre (HU). ÜRÖGDI, László [HU/HU]; Teleki u. 80, H-1184 Budapest (HU). MÁRVÁNYOS, Ede [HU/HU]; Béke tér 5, H-1139 Budapest (HU). BARABÁS, Mihály [HU/HU]; Egry J. u. 36, H-1111 Budapest (HU). KURUCZ, István [HU/HU]; Balzac u. 12 II 25, H-1136 Budapest (HU). BÁCSY, Ernő [HU/HU]; Bor u. 2, H-1119 Budapest (HU). KORÁNYI, László [HU/HU]; Hermann O. u. 10, H-1022 Budapest (HU). ERDŐ, Sándor [HU/HU]; Kléh I. u. 3/B, H-1126 Budapest (HU). DORMÁN, György [HU/HU]; Kondorosi u. 15 fsz. 4, H-1116 Budapest (HU). VITAI, Márta [HU/HU]; Udvarbíró tér 3, H-8330 Sümeg (HU). SCHMIDT, György</p> </div> <div style="width: 48%;"> <p>[HU/HU]; Karinthy u. 9, H-1111 Budapest (HU). SINKA, Márta [HU/HU]; Kassai u. 71, H-1142 Budapest (HU).</p> <p>(74) Agent: S.B.G. AND K. PATENT AND LAW OFFICE; Andrássy út 113, H-1062 Budapest (HU).</p> <p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> </div> </div>		
<p>(54) Title: PHARMACEUTICAL PRODUCTS FOR CURING AND PREVENTING ILLNESSES CONNECTED WITH THE MALFUNCTION OF VASCULAR ENDOTHELIAL CELLS</p> <p>(57) Abstract</p> <p>The invention relates to the use of certain hydroxylamine derivatives in the therapy or prevention of illnesses connected with the dysfunction of the vascular endothelial cells. Another object of the invention is the use of the same compounds in the preparation of pharmaceutical compositions against the above diseases. In general formulae (I) and (II), R<sup>1</sup> and R<sup>2</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom in-between form a saturated 5 - 7 membered heterocyclic group, containing optionally further nitrogen and/or oxygen heteroatoms, A refers to a straight or branched alkyl group of 4 to 12 carbon atoms, a phenyl group, substituted or unsubstituted, containing preferably an alkyl-, haloalkyl- or nitro group as substituent, or a 5 - 6 membered heteroaromatic ring containing nitrogen, oxygen or sulphur, in general formula (I), Z refers to a covalent bond, and in general formula (II) to a covalent bond or a =NH group, in general formula (I), X refers to a halogen atom or to a - NR<sup>3</sup>R<sup>4</sup> group, wherein R<sup>3</sup> and R<sup>4</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, while in general formula (II) X refers to an oxygen atom, in general formula (II), R<sup>1</sup> refers to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, and in general formulae (I) and (II), Y refers to a hydrogen atom, a hydroxyl group or an acyloxy group, which contains preferably the acyl part of a long chain fatty acid of 8 to 22 carbon atoms, or of a cyclic aromatic carboxylic acid as its acyl component, and in the compounds of general formula (I) wherein X refers to a - NR<sup>3</sup>R<sup>4</sup> group and Y refers to a hydroxyl group, the X group is condensed with the Y substituent and forms the intramolecular ring represented by general formula (III), in which formula A, Z, R<sup>1</sup> and R<sup>2</sup> have the same reference as above.</p>		



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Pharmaceutical Products for Curing and Preventing Illnesses Connected with the Malfunction  
of Vascular Endothelial Cells

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Technical field of the invention

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The invention concerns products for curing or preventing illnesses connected with the dysfunction of the vascular endothelial cells, which contain a hydroxylamine-derivative of general formula (I) or (II) as the effective agent.

15

Background of the invention

The normal functioning of the vascular endothelial cells is of crucial importance for the body. These cells form an edge surface between the circulating blood and the elements of the vein wall performing thrombogenous activity. The role of the vascular endothelial cells in homeostasis is quite varied:

- they participate in the two-way transport of substances originating from the blood and the tissues,
- they form a barrier for the macromolecules,
- 25 - these cells are the location of the synthesis and the decomposition of the mediators acting in the regulation of the interaction between the cellular elements of the vein wall and the blood (e.g. fibrinogen, collagen, proteoglycans, PGI<sub>2</sub>, EDRF (NO), EDHF, endothelin-1, angiotensin-II),
- they initiate the migrational, proliferative, and thrombolytic processes contributing to histi-
- 30 reparation,
- they sustain the thromboresistance of the vein wall [Rubányi, G., J. Cardiovasc. Pharmacol. 1993, 22 (42. Suppl., p S1 - 14]

The impairment of the endothelium results in atherosclerosis. The impairment leading to the deterioration of the endothelium can occur at mechanic intervention, for example catheterisation, and also as the result of biochemical and immunological processes.

35

As the first step of the formation of atherosclerotic plaque, cells filled with lipids accumulate in the intima of the arteries (Steinberg D. et al., JAMA 264-304, 1990). These

cells - especially monocytes and macrophages originating from the blood - first stick to the endothelium, and then penetrate the intima. The injury of the endothelial cells may also contribute to the adhesion, although no morphological alteration is visible in the early phase. The oxidation of the LDL particles may result in their incorporation by the monocytes located in the intima, and the monocytes thus become foam cells. These foam cells form the lipid-streaks, the earliest form of arteriosclerotic alteration.

In the later stages, bleeding, necrosis, neovascularisation, and sclerosis occur, and in the course of these, the intergrown plaque forms, which then taper the arteries (Ip. JH, Fuster et al., J. Am. Coll. Cardiol 15:1667, 1990).

Thrombosis may occur at various stages of atherosclerosis. Repeated thrombosis leads to vascular obstruction and thromboembolic illnesses, such as coronary thrombosis, the thrombosis of the brain vessels, or peripheral vascular illnesses.

In a clinical sense, "endothelial dysfunction syndrome" refers to generalised or localised vessel spasm, thrombosis, arteriosclerosis, and restenosis. Attempts to cure these illnesses have included interventional clinical techniques, bypass surgery, and medicinal treatment.

Only a few existing drugs may be suitable for the "treatment" of endothelial dysfunction. They fall into four major categories:

- substitution for natural "protective" endothelial substances (e.g. stable analogues of PGI<sub>2</sub>, nitro-vasodilators, rt-PA /recombinant tissue plasminogen activator/)
- inhibitors or antagonists of endothelium-derived contracting factors (e.g. ACE inhibitors, angiotensin II receptor antagonists; TXA<sub>2</sub>-receptor antagonists)
- cytoprotective agents (e.g. the free-radical scavengers superoxide dismutase and probucol, and free radical production inhibitor lazaroids)
- lipid-lowering drugs.

Although none of them were originally designed for this target, their already proven clinically beneficial effects in the case of certain illnesses may involve the protection or restoration of normal endothelial function. The rationale behind innovative therapies in this category is the restoration of normal endothelial cell lining, where these cells themselves will "do the job". Potential approaches may include stimulation of regrowth of normal endothelium, or by new emerging therapeutic modalities based on recombinant DNA technology (Science 1990; 249: 1285-8). According to the data available, no recognised drug fulfils these criteria.

These days no medicine or medicine-candidate is known to act directly on the endothelium, and thus none is suitable for treating endothelial dysfunction. Therefore, there is great therapeutical demand for a medicine which is capable of preventing, reversing, or at

least slowing down the formation of complication symptoms, or decreasing the occurrence of the illness.

5 Summary of the invention

In the course of our research we have found that the hydroxylamine-derivatives of general formula (I) and (II) perform a strong protecting and regenerative effect on vascular endothelial cells, and are capable of preventing their impairment of various origins.

10 In the general formulae (I) and (II),  $R^1$  and  $R^2$  independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, or  $R^1$  and  $R^2$  together with the nitrogen atom in-between form a saturated 5 - 7 membered heterocyclic group, containing optionally further nitrogen and/or oxygen heteroatoms,

A refers to a straight or branched alkyl group of 4 to 12 carbon atoms, a phenyl group, 15 substituted or unsubstituted, containing preferably an alkyl-, haloalkyl- or nitro group as substituent, or a 5 - 6 membered heteroaromatic ring containing nitrogen, oxygen or sulphur, in the compounds of general formula (I), Z refers to a covalent bond, and in the compounds of general formula (II) to a covalent bond or a =NH group,

in the compounds of general formula (I), X refers to a halogen atom or to a -  $NR^3R^4$  group, 20 wherein  $R^3$  and  $R^4$  independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, while in the compounds of general formula (II) X refers to an oxygen atom,

in the compounds of general formula (II),  $R'$  refers to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, and

25 in general formulae (I) and (II), Y refers to a hydrogen atom, a hydroxyl group or an acyloxy group, which contains preferably the acyl part of a long chain fatty acid of 8 to 22 carbon atoms, or of a cyclic aromatic carboxylic acid as its acyl component, and in the compounds of general formula (I) wherein X refers to a -  $NR^3R^4$  group and Y refers to a hydroxyl group, the X group is condensed with the Y substituent and forms an 30 intramolecular ring.

The salts and the optically active forms of these compounds are also effective compounds.

Those compounds of general formula (I) that have X referring to a - $NH_2$  group, and A referring to an unsubstituted phenyl- or pyridyl-group, and in which Y refers to a hydroxyl 35 group are already known from the published French patent application of No.2362 845 A1. These compounds are, according to the above quoted patent application, selective beta-blockers, and are thus suitable for the treatment of diabetic angiopathy.

Those compounds of general formula (I) that have X referring to a halogen atom, Y referring to a hydroxyl group, and A to an unsubstituted or substituted phenyl- or pyridyl-group are already known from the published PCT patent application of No. WO 90/04584 A1. These compounds have a selective beta-blocking effect, and are thus suitable as effective agents in the treatment of diabetic angiopathy.

Those compounds of general formula (II) that have A referring to a phenyl- (unsubstituted or substituted by a haloalkyl-group), pyridyl-, or thienyl-group, Z referring to a covalent bond, R' referring to a hydrogen atom, and Y to a hydroxyl group are already known from the Hungarian patent application of No. 2385/92, published under No. T/66350. These compounds have an anti-ischaemic and anti-anginetic effect, and are thus well usable in the therapy of vein complications connected with diabetes mellitus.

Those compounds of general formula (I) that have A referring to an aromatic or heteroaromatic ring and X to a halogen atom, while Y refers to a hydrogen atom are already known from the published PCT patent application of No. WO 95/30649 A1. These compounds are of an anti-ischaemic effect, and can be best used in the treatment of the occurrences of ischaemia of which hypertonic veins and thrombocyte aggregation are characteristic.

In none of the above quoted specifications is it written that the described compounds should have any effect on the vascular endothelial cells.

As we have mentioned above, our research has proved the compounds of general formulae (I) and (II) to be effective on the endothelial cells of the cardiovascular and the cerebrovascular systems. In the experiments to be dealt with in detail later, it has been observed that these compounds are capable of blocking or restoring the damaging of these cells. Thus, these compounds may be used as effective substance in therapeutical products which are used in the treatment of illnesses resulting from the abnormal functioning or the damaging of the endothelial cells, especially cardiovascular and cerebrovascular illnesses, hypertension, hyperhomocysteinaemia, and peripheral vascular diseases.

Based on this observation, the invention consists of the application of the hydroxylamine derivatives of general formulae (I) and (II) - wherein R<sup>1</sup> and R<sup>2</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom in-between form a saturated 5 - 7 membered heterocyclic group, containing optionally further nitrogen and/or oxygen heteroatoms, A refers to a straight or branched alkyl group of 4 to 12 carbon atoms, a phenyl group, substituted or unsubstituted, containing preferably an alkyl-, haloalkyl- or nitro group as substituent, or a 5 - 6 membered heteroaromatic ring containing nitrogen, oxygen or sulphur,

in general formula (I), Z refers to a covalent bond, and in general formula (II) to a covalent bond or a =NH group,

in general formula (I), X refers to a halogen atom or to a -NR<sup>3</sup>R<sup>4</sup> group, wherein R<sup>3</sup> and R<sup>4</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, while in general formula (II) X refers to an oxygen atom,

in general formula (II), R' refers to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, and

in general formulae (I) and (II), Y refers to a hydrogen atom, a hydroxyl group or an acyloxy group, which contains preferably the acyl part of a long chain fatty acid of 8

to 22 carbon atoms, or of a cyclic aromatic carboxylic acid as its acyl component,

however, in certain types of compounds of general formula (I) wherein X refers to a -NR<sup>3</sup>R<sup>4</sup> group and Y refers to a hydroxyl group, the X group is condensed with the Y substituent and forms the intramolecular ring represented by general formula (III), in which formula A, Z, R<sup>1</sup> and R<sup>2</sup> have the same reference as above,

furthermore, of the salts and optically active forms of these compounds for the production of medicine used for the treatment or prevention of illnesses connected with the dysfunction of the endothelial cells.

The invention also relates to pharmaceutical products used for the treatment and prevention of illnesses in connection with abnormal functioning of the vascular cells which contain, as effective substance (apart from the usual carrier substances and auxiliary substances used in pharmaceutical compositions) a compound of general formula (I) or (II) in 0.5-95.5 m/m %, or in certain cases the salts or optically active forms of these compounds, and in these formulae the references of R<sup>1</sup>, R<sup>2</sup>, A, Z, X, Y and R' are the same as above.

Those compounds of general formula (I) and (II) are preferred for the application described in the invention, wherein A refers to a pyridyl-, a thienyl-, or a phenyl-, nitrophenyl- or trifluoromethylphenyl group. Those compounds of general formula (I) are also preferred wherein X refers to a chloro atom or to a NH<sub>2</sub> group. Of these latter compounds particularly preferred are those which contain an intramolecular ring formed by the condensation of groups X and Y. Also preferred are those compounds of general formula (II), wherein R' refers to a hydrogen atom, and those compounds of general formula (I) or (II) wherein Y refers to a hydrogen atom or a hydroxyl group. In all these listed categories preferred are those compounds wherein the NR<sup>1</sup>R<sup>2</sup> group refers to a piperidino- or dialkylamino group.

The following compounds of general formula (I) and (II) are especially preferred for the invention:

N-[2-benzoyloxy-3-(1-piperidinyloxy)propoxy]-3-pyridinecarboximidamide  
(Z)-2-butenedioate (1:1) (compound No. 1.)

- N-[2-palmitoyloxy-3-(1-piperidinyloxy)propoxy]-3-pyridinecarboximidamide monohydrochloride (compound No. 2.)
- N-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3-trifluoromethylbenzene-carboximidoyl chloride monohydrochloride (compound No. 3.)
- 5 N-[2-hydroxy-3-(1-piperidinyloxy)propoxy]-2-thiophenecarboximidoyl chloride monohydrochloride (compound No. 4.)
- N-[2-hydroxy-3-(1-piperidinyloxy)propoxy]-benzenecarboximidoyl chloride monohydrochloride (compound No. 5.)
- N-[2-hydroxy-3-(1-piperidinyloxy)propoxy]-4-pyridinecarboximidoyl chloride
- 10 (Z)-2-butenedioate (1:1) (compound No. 6.)
- N-[2-hydroxy-3-(1-piperidinyloxy)propoxy]-2-nitrobenzenecarboximidoyl chloride monohydrochloride (compound No. 7.)
- N-[3-(1-piperidinyloxy)propoxy]-3-pyridinecarboximidoyl chloride dihydrochloride (compound No. 8.)
- 15 N-[3-(1-piperidinyloxy)propoxy]-3-nitrobenzenecarboximidoyl chloride Monohydrochloride (compound No. 9.)
- N-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3-trifluoromethylbenzamide (compound No. 10.)
- N-hexyl-N'-[2-hydroxy-3-(1-piperidinyloxy)propoxy]-urea (compound No. 11.)
- 20 N-hexyl-N'-[3-(1-piperidinyloxy)propoxy]-urea (compound No. 12.)
- 5,6-dihydro-5-(1-piperidinyloxy)methyl-3-(3-pyridyl)-4H-1,2,4-oxadiazine (compound No. 13.)

Those compound of general formula (I) in which X refers to halogen atom may be

25 prepared by reacting an amidoxim of general formula (V), wherein A has the same reference as above with an amino-chloro-propane derivative, wherein R<sup>1</sup>, R<sup>2</sup> and Y have the same references as above and the -NH<sub>2</sub> group of the resulting intermediate of general formula (IV), wherein Z refers to covalent bond while the other substituents have the same references as above is replaced with a halogen atom by diazotation. In cases when a compound of general

30 formula (I) containing a hydroxyl group as Y substituent is produced the necessary amino-chloro-propane derivative of general formula (XII) containing a hydroxyl group as Y substituent may be produced from epichlorohydrin of formula (VI) and an amine of general formula (IX), wherein R<sup>1</sup> and R<sup>2</sup> have the same references as above. An alternative procedure is to react the epichlorohydrine with the amidoxim of general formula (V) first, and then to

35 diazotate the resulting intermediate of general formula (VII), wherein A refers to the same as above and to react the epoxy-compound of general formula (VIII), wherein A refers to the same as above with the amine of general formula (IX).



Those compounds of general formula (I), wherein Y refers to an acyloxy group may be produced by a reaction of the suitable compounds of general formula (I) containing a hydroxyl group in the place of Y, and acid chlorides of general formula (XI), wherein R<sup>5</sup> refers to a long chain alkyl or to an aryl group.

5       The compounds of general formula (II) containing covalent bonds in the place of Z may be produced by one of the following methods:

(i) connecting an alkali-hydroxamate of general formula (XIII) wherein A and R' have the same reference as above and K refers to the cation of an alkaline metal, and a halogen compound of general formula (XII) wherein R<sup>1</sup>, R<sup>2</sup> and Y have the same references as above,  
10   or

(ii) the reaction of an amino compound of general formula (XIV) wherein R<sup>1</sup>, R<sup>2</sup>, Y and R' have the same reference as above, and an acid halogenide wherein A has the same reference as above,

while those compounds of general formula (II) which contain a covalent bond in the place of Z, and a hydrogen atom in the place of R' may also be produced – beyond methods  
15   (i) and (ii) - by the following methods:

(iii) the diazotation in a halogen-free environment of a suitable compound of general formula (I) containing a -NH<sub>2</sub> group in the place of X, and a covalent bond in the place of Z,  
or

20   (iv) the hydrolysis of a suitable compound of general formula (I) containing a halogen atom in the place of X.

Those compounds of general formula (II) wherein A refers to an alkyl group and Z refers to a =NH group may be produced by the reaction of a compound of general formula (II) wherein R<sup>1</sup>, R<sup>2</sup>, Y and R' have the same references as above, in an organic solvent,  
25   preferably in chloroform, with an equimolar amount of alkylisocyanate wherein A refers to an alkyl group.

The compounds of general formula (III) are special cases of the compounds of general formula (I) wherein a nitrogen containing X group is condensed with the Y substituent to form an intramolecular ring.

30   Such compounds may be produced by the reaction of a compound of general formula (I) (wherein Y refers to a hydroxyl group) with an excess of thionyl chloride, followed by the ring closure of the resulting intermediate compound of general formula (IV) (wherein Y refers to a chlorine atom, while the other substituents have the same references as above) with an excess of potassium-terc-butoxide boiled in an organic solvent (preferably in t-butanol).

35   The hydroxylamine derivatives of the invention bear surprising pharmacological properties. It is to be noted especially, that they do not only regenerate the endothelial cells morphologically, but also functionally, that is, due to their effect the endothelial cells of the

good tolerability of these compounds is also remarkable. These characteristics form the grounds for the pharmaceutical use of the hydroxylamine derivatives of general formulae (I) and (II). These medicines may be used to treat cardio- and cerebrovascular illnesses of humans and animals, such as hypertension, hyperhomocysteinaemia and peripheral vascular illnesses.

Among cardiovascular illnesses, these compounds may be best used in the cases of coronary artery illnesses, atherosclerosis, restenosis following catheterisation, and coronary bypass surgery, and among cerebrovascular illnesses in the cases of cerebral artery occlusion, the hydroxylamine derivatives of general formulae (I) and (II) may also be applied, in the treatment of hypertension against cases resulting from essential, renal, pulmonal and endocrine illnesses, while in the therapy of peripheral vascular illnesses they are best used when aortic stenosis occurs in the legs.

The compounds of the invention may also be used to counteract susceptibility for illness due to the genetically determined or temporary weakening of the protective mechanism. The usual dose depends on the patient treated and the illness in hand and may vary in the range of 0.1 – 200 mg/kg, preferably of 1-50 mg/kg, daily. This may mean, for example, that a daily dose for human therapy is between 10 to 200 mg orally, 1 to 15 mg rectally, or 2 to 20 mg parenterally, for adult patients.

Suitable pharmaceutical compositions may be for example solid substances or liquids, in any kind of drug formulations generally used in human or veterinary therapy, such as simple or coated tablet, gel capsule, granulates, solution, syrup, suppository, lyophilised or not lyophilised injectable product; these may be produced by the usual methods. The effective substance may be carried by the vehicles usual for these types of pharmaceutical products, such as talc, gum Arabic, lactose, starch, magnesium stearate, cocoa-butter, aqueous or non-aqueous carriers, animal or plant greases, paraffin derivatives, glycols, various moistening, dispersing, or emulgating substances and preservatives.

The biological effects of the compounds of the invention represented by the general formulae (I) and (II) are illustrated through the following results of the vein relaxational effect test performed in vitro on rats, and of the toracic aorta morphological test. Three-month-old, genetically hypertonic (SH) Wistar Okamoto rats were treated for 1 month with the various tested compounds, followed by functional and morphological examinations.

#### THE VEIN RELAXING EFFECT OF THE TESTED HYDROXYLAMINE DERIVATIVES ON THE TORACIC AORTA OF THE SH RATS (IN VITRO TEST)

The test was performed according to the method known from the applying literature [Japan J. Pharmacol., 59, 339-347 (1992)]. The SH rats were narcotised with Nembutal (40

mg/kg, i.p.), and their toracic aorta was then taken out and placed in an oxygenated (95% O<sub>2</sub> + 5% CO<sub>2</sub>) Krebs-Henseleit solution. The composition of the solution (mM): NaCl 118, KCl 4, 7, CaCl<sub>2</sub> 2.52, MgSO<sub>4</sub> 1.64, NaHCO<sub>3</sub> 24.88, KH<sub>2</sub>PO<sub>4</sub> 1.18, glucose 5.5. The 3 mm long vein rings were suspended in a 20ml organ bath of 37°C. The resting tension was 1g, which was sustained throughout the experiment. During the 1 hour equilibration period the medium of the organ bath was changed every 20 minutes. The veins were contracted with 10<sup>-6</sup> M methoxamine (approx. 80% of max. contraction). After reaching the maximum contraction, the vasodilation provoked by acetylcholine (Ach) (10<sup>-6</sup> - 10<sup>-4</sup> M) was examined, which was informative of the condition of the endothelium of the vein wall. The contraction force was measured with an isometric strain gauge (SG-01D, Experimetria Ltd), and registered on an OH-850 polygraph (Radelkis). The results of the tests are summarised in table No. 1.

Table 1

The vein relaxing effect of the compounds of the invention on the toracic aorta of SH rats (in vitro test)

Substances/Doses	Ach doses (M)		
	10 <sup>-6</sup>	10 <sup>-5</sup>	10 <sup>-4</sup>
SH control, n=10	53.8	55.6	71.0
Compound no.13., n=12; 20 mg/kg	79.6	86.0	95.9
Compound no. 5., n=11; 5 mg/kg	82.3	84.5	87.2
Compound no. 4., n=11; 20 mg/kg	75.6	79.8	80.5
Compound no. 6., n=10; 5 mg/kg	87.5	87.9	84.4
Compound no. 10., n=12; 10 mg/kg	64.8	63.7	78.0
Compound no. 1., n=12; 20 mg/kg	74.7	58.7	82.7
Compound no. 2., n=10	80.4	75.6	88.0
Compound no. 11., n=12; 20 mg/kg	88.1	91.3	91.9
Compound no. 8., n=10; 5 mg/kg	74.1	75.3	80.9
Compound no. 3., n=8; 10 mg/kg	76.4	77.2	84.8
Compound no. 12., n=12; 10 mg/kg	66.3	67.2	84.1
Compound no.7., n=11; 5 mg/kg	81.7	86.0	95.9
Captopril, n=8; 20 mg/kg	88.7	88.2	94.2

As it is apparent from the table, in the cases of untreated hypertonic control animals the relaxation, provoked by the administration of 10<sup>-4</sup> M acetylcholine decreased to 71%.

which is due to the endothelium damage caused by hypertension. The tested compounds improved this decreasing vasodilation significantly, which shows the improvement of the endothelial function.

5 THE MORPHOLOGICAL EXAMINATION OF THE TORACIC AORTA WITH ELECTRONMICROSCOPE

10 This test was performed according to the applying literature (Br. J. of Pharmacol., 1995; 115, 415-420). 1mm<sup>2</sup> segments of the aorta-wall of the toracic aorta of the rats were cut out, which were then fixed at room temperature with 2.5% glutaraldehyde. This was followed by a post-fixation with 1% osmium tetroxide, which lasted for one hour. Afterwards, the tissue segments were dehydrated with ethanol, and bedded into Durcupan ACM. The excisions were evaluated in a qualitative manner based on the photograph taken on a Hitachi 7100 electronmicroscope. The results of these tests are shown in table No. 2.

15 The results of the morphological tests were expressed on a scale of 1 to 5, depending on the extent to which the treatment with the tested compounds restored the endothelial damage caused by hypertension, that is, the extent of regenerating activity. On the scale, 1 represents cases where there was no regeneration to be observed, 2 stands for weak, 3 for medium, 4 for good, while 5 represents strong regeneration.

20 In comparison with the untreated control significant protective or regenerative effect was observed after treatment with the hydroxylamine derivatives of general formulae (I) and (II) of the invention. Due to the treatment, a thin protective layer formed over the injured subendothelium, which was composed of cells containing an active nucleus and rich cytoplasm. Regeneration appeared quite effective in the majority of the cases.

Table 2.  
The electromicroscopic evaluation of the effects of the compounds of the invention  
on the toracic aorta of SH rats (morphological test)

Substances Doses	Extent of Regeneration
SH control (phys. salt)	1
Compound no. 13., 20 mg/kg p.o.	5
Compound no. 5., 5 mg/kg p.o.	5
Compound no. 4., 5 mg/kg p.o.	5
Compound no. 10., 10 mg/kg p.o.	4
Compound no. 1., 20 mg/kg p.o.	3
Compound no. 11., 20 mg/kg p.o.	4
Compound no. 8., 5 mg/kg p.o.	3
Compound no. 9., 5 mg/kg p.o.	3
Compound no. 12., 5 mg/kg p.o.	4
Compound no. 14., 20 mg/kg p.o.	3
Captopril 100 mg/kg p.o.	3

These experimental data also support the assumption that the compounds of general formula (I) and (II) are able to regenerate the endothelium not only functionally but morphologically as well. Upon chronic treatment these compounds resulted in more pronounced morphological regeneration than the reference substance Captopril.

#### EXAMINATION OF THE INFARCTED AREA ON SPONTANEOUSLY HYPERTENSIVE (SH) RATS AFTER ONE MONTH ORAL TREATMENT

##### Experimental groups

1. SH-age matched control
2. Verapamil ( as a reference drug), 50 mg/kg p.o.
3. Compound No. 13., 20 mg/kg p.o.
4. Compound No. 13., 50 mg/kg p.o.
5. Compound No. 5., 5 mg/kg p.o.
6. Compound No. 4., 5 mg/kg p.o.

### Induction of infarction

Myocardial ischaemia was induced by a temporary occlusion of the main left coronary artery, according to Griswold et al. (J. Pharmacol. Methods 1988. 20: 225-35). SH rats were anaesthetized with sodium pentobarbital (50 mg/kg i.p.). After tracheotomy, the animals were ventilated with room air by a respirator for small rodents (model: Harvard 552), with a stroke volume of 1,5-2 ml/100 g and a rate of 55 strokes/min to maintain normal  $pO_2$ ,  $pCO_2$  and pH parameters.

The right carotid artery was catheterised and connected with a pressure transducer (P236B Stetham) for the measurement of systemic arterial blood pressure (BP) by means of a preamplifier (Hg-O2D Experimetria<sup>R</sup>). Heart rate (HR) was measured by a cardiometer (HR-01, Experimetria<sup>R</sup>). The electrocardiogram (ECG standard lead III.) was recorded on a devices recorder (ER- 14, Micromed<sup>R</sup>) by means of subcutaneous steel needle electrodes. The chest was opened by a left thoracotomy and the heart was exteriorized by a gentle pressure on the right side of the rib cage.

A 4/0 silk ligature was quickly placed under the main left coronary artery. The heart was replaced in the chest and the animal left to recover.

Rectal temperature was monitored and was maintained constant at 37°C.

The experimental protocol was initiated with a 15 min stabilisation period during which the observation of a sustained blood pressure less than 70 mmHg and/or the occurrence of arrhythmias lead to exclusion.

Myocardial ischaemia was induced with coronary artery occlusion for 1 hour and reperfusion allowed for 1 hour. Sham operated animals underwent to all the previously described surgical procedures except coronary occlusion and reperfusion.

### Quantification of myocardial infarction

At the end of experiment, the heart was quickly removed. The left ventricle was sliced into 2 mm thick sections parallel to the atrioventricular groove. The slices were incubated in a 0.1% solution of Nitroblue Tetrazolium grade III, pH 7,4 for 15 min. The non-infarcted area was colored blue due to formation of a precipitate that results from reaction of NBT with dehydrogenase enzymes. Loss of these enzymes from infarcted myocardium prevents formation of the precipitate; thus, the infarcted area within the risk region remains pale yellow. The LV sections were photographed (Practica) and infarcted area was measured by planimetry. The necrotic area was expressed as a percentage of the surface of the left ventricle.

### Statistical analysis

All values will be expressed as mean  $\pm$ SEM. Comparisons between groups will be assessed by one-way ANOVA with post hoc analysis using the Student „t” test. Statistical significance will be defined as  $p < 0.05$ .

### Results

There was no significant difference in the haemodynamic parameters, left ventricular and body weights among the groups.

Table 3.  
The infarct size and the survival rate of SH rats after coronary artery occlusion and reperfusion

Groups	Infarct size (%)	Survival rate (%)
Control n = 9	42.7 $\pm$ 1.37	28.13
Verapamil 50mg/kg n = 8	24.3 $\pm$ 2.87**	53.3**
Compound No. 13. 20mg/kg, n = 7	22.3 $\pm$ 3.6**, #	77.8**, #
Compound No. 13. 50mg/kg, n = 5	15.2 $\pm$ 3.7**	60.0**
Compound No. 5. 5mg/kg, n = 3	29.3 $\pm$ 2.9**	30.0
Compound No. 4. 5 mg/kg, n = 5	25.6 $\pm$ 4.0**	71.4**, #

\*\* $p < 0.01$  vs control #  $p < 0.01$  vs verapamil

Following coronary artery occlusion and reperfusion, there was a marked decrease in the survival rate of the control rats. Administration of different active compounds (except compound No. 5.) and the reference substance verapamil orally for one month significantly increased the resistance of rats to myocardial ischaemia/reperfusion injury.

Compared to verapamil, the improvement was significantly higher after treatment with compound No. 13. (20 mg/kg) and compound No. 4.

The active compounds and verapamil significantly reduced the infarct size compared to the control animals. The infarct size limitation was dose-dependent. The higher dose significantly reduced the extension of the myocardial necrosis compared to verapamil.

Our experiments indicate that selected active compounds significantly reduced the extension of the myocardial necrosis and significantly improved the survival rate. Infarct size limitation occurred without any marked changes in the haemodynamic parameters, and it was

significantly higher after treatment with the compounds of the invention than after administration of the reference substance verapamil.

#### WOUNDING MIGRATION ASSAY

5 HUVEC cells were isolated and cultivated according to Jaffe E. A. et al. (J. Clin. Invest., 52, 2745-2756, 1973) The assay was carried out as described by Yamamura S. et al. (J. Surg. Res., 63, 349-354, 1996). HUVEC cells were seeded on 96 well plate, previously coated with fibronectin (2µg/well)(Sigma), and at appr.90% confluency the monolayer was wounded  
10 along by coordinate line labeled backside of the plate. The layer injured with a Teflon cell scraper that was 1 mm in width. Well was rinsed and filled with completed RPMI 1640 medium (containing 5% of protein) for incubation (at 37°C in 5% CO<sub>2</sub> containing air). Cells were allowed to migrate for 24 and 48 hours onto the wounded field and camera or photographs were taken through an inverted microscope (at x60 magnification) to recording.  
15 The numbers of cells that were moved beyond the reference line counted and evaluated by image analyzer.

#### Treatment with the test compound

A serial ten step fold dilution were prepared in medium added 5 µl/well containing 95 µl of tissue culture over the wounded cell monolayer. The control culture contained no dilution of  
20 compound No. 13..

#### Results

After 24 hour incubation the cells spontaneously appeared in the wounded area and even an increased number was counted in the presence of test compound at a submicromolar  
25 concentration (at 10<sup>-7</sup> and 10<sup>-8</sup> M). test compound resulted an emphatic, considerable promotion on cell migration even 48hrs period. The wounded area was covered about 82% compared to 47% with the spontaneous migrated human endothelial cells.

Table 4.  
Results of the wounding migration test with compound No. 13.

Doses 10 <sup>-x</sup> (M)	The covered area			
	cell/mm <sup>2</sup>		%/mm <sup>2</sup>	
	24 h	48 h	24 h	48 h
7	689	1009	56	82
8	750	948	61	80
Non-treated*	480	578	39	47



Adhered cells**	180	6
* Non treated control, spontaneous migration,		
** Cells on the injured surface immediately after wounding start, control situation.		

- 5 The repair process of damaged vascular monolayer is started with migration of endothelial cells by that way may further initialized reconstruction of injured area. All our data suggest that test compound may promote repair on wounded human endothelial cells with direct enhancement of migration.
- 10 The invention is illustrated in the following examples without any limitation on the scope claimed:

#### Detailed description of the preferred embodiments

##### 15 *Example 1:*

**N-[2-benzoyloxy-3-(1-piperidiny)propoxy]-3-pyridinecarboximidamide (Z)-2-butenedioate (1:1)** (compound No. 1.)

##### Procedure:

- 20 20.9 g (75.0 mmol) of N-[2-hydroxy-3-(1-piperidiny)propoxy]-3-pyridine-carboximidamide [Hung. Pat. 177.578 (1976)] was dissolved in 300 ml of benzene. To this solution 150 ml of 1 N sodium hydroxide solution was added, followed by dropwise addition of 19.5 ml (168 mmol) of benzoylchloride. After stirring the mixture intensively for 2 hours, 7.1 g (67 mmol) of sodium carbonate and a further portion of benzoylchloride (9.75 ml; 84 mmol) was added,
- 25 and the stirring was continued overnight. The phases were then separated, the organic layer was extracted with 1 N sodium hydroxide solution and water, dried and evaporated to dryness. The residue (41 g oil) was dissolved in 150 ml of acetone, and 8.7 g (75 mmol) maleic acid was added. The obtained precipitate was filtered off, washed with acetone, and dried.
- Yield: 29.0 g (78 %)
- 30 Mp.: 194-195 °C

##### *Example 2:*

**N-[2-palmitoyloxy-3-(1-piperidiny)propoxy]-3-pyridinecarboximidamide monohydrochloride** (compound No. 2.)

35

##### Procedure:

14.7 g (52.8 mmol) of N-[2-hydroxy-3-(1-piperidinyl)propoxy]-3-pyridine-carboximidamide [Hung. Pat. 177.578 (1976)] was dissolved in 160 ml of chloroform. 7.7 ml (55 mmol) of triethylamine was added, followed by dropwise addition of a solution of palmitoylchloride (14.7 g; 56.5 mmol) in 85 ml of chloroform. The mixture was stirred overnight at room temperature. Next day further amount of 3.8 ml of triethylamine and 7.4 g of palmitoylchloride was added, and the stirring was continued for one more day. The solution was extracted then with water, 5 % acetic acid and water, successively, dried over anh. sodium sulphate, and evaporated to dryness.

The residue (28.2 g oil) was dissolved in ethyl acetate, and the product was precipitated by addition of 30 ml of 1 N HCl/ethyl acetate. The thick, white precipitate was filtered off, washed with ethyl acetate and dried.

Yield: 10.9 g (37 %)

Mp.: 110-113 °C

*Example 3:*

N-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3-trifluoromethylbenzene-carboximidoyl chloride monohydrochloride (compound No. 3.)

Procedure:

Step a)

50 g (0.245 mol) of m-trifluoromethyl-benzamidoxime and 33.7 g (0.6 mol) of potassium hydroxide was dissolved in a mixture of dimethyl sulphoxide and 170 ml of water, and the mixture was cooled to 0 °C. 48 ml (0.6 mol) of epichlorohydrin was added, and the reaction mixture was stirred at 0 °C for 5 hours, then kept in a refrigerator overnight. Next day 250 ml of water was added, and the mixture was extracted with ethyl acetate (4x250 ml). The combined organic phases were washed with water, dried, treated with charcoal and evaporated to dryness, to yield m-trifluoromethyl--N-(2,3--epoxypropoxy)-benzamidine, as a colourless oil.

Yield: 61 g (96 %)

Step b)

To the obtained oil 400 ml of 18 % of hydrochloric acid solution and 60 ml of ether were added, and the mixture was cooled to -5 °C, while stirring. 17.4 g (0.25 mol) of sodium nitrite, dissolved in 60 ml of water was added slowly in 40 min., and the reaction mixture was stirred for another 20 minutes. The mixture was extracted then with ether (2x160 ml), and the combined organic phases were washed with water twice. To the ethereal solution 340 ml of 20 % of sodium hydroxide solution was added, and the two-phase system was refluxed for 1 hour, while stirring. The phases were then separated, the organic layer was washed with brine

until neutral, dried and evaporated to dryness to give m-trifluoromethyl-N-(2,3-epoxypropoxy)-benzimidoyl chloride, as a colourless oil.

Yield: 30.5 g (45 %)

Step c)

5 A mixture of 1.19 g (4.2 mmol) N-[(2,3-epoxy)propoxy]-3-trifluoromethyl-benzenecarboximidoyl chloride and 0.89 ml (8.5 mmol) of *tert*-butylamine in 12 ml of isopropyl alcohol was refluxed for 2 hours. Solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, and 0.98 ml of methanolic hydrogen chloride solution (4.3 N) was added and the mixture was concentrated to small volume under vacuum, then  
10 diluted with ether. The precipitate that formed was recovered, washed with cold ether and dried.

Yield: 0.48 g (32 %)

Mp.: 150-153 °C

IR (KBr): 3423, 3233, 2978, 2880, 2784, 1620, 1570, 1479, 1441, 1400, 1383, 1340,  
15 1238, 1167, 1128, 1101, 1072, 1038, 982, 930, 897, 804, 787, 714, 694 cm<sup>-1</sup>

*Example 4:*

**N-[2-hydroxy-3-(1-piperidiny)propoxy]-2-thiophenecarboximidoyl chloride monohydrochloride** (compound No. 4.)

20

Procedure:

5.0 g (15.6 mmol) of N-[2-hydroxy-3-(1-piperidiny)propoxy]-2-thiophenecarboximidamide monohydrochloride was dissolved in 19 ml of water, then 6.1 ml of concentrated hydrochloric acid was added. The solution was cooled to -5 °C, then a cold solution of 4.4 g  
25 (63.8 mmol) of sodium nitrite in 2.4 ml of water was added dropwise. Throughout the reaction the internal temperature was maintained at 0 °C. When addition was completed the mixture was stirred for a further one hour. Cold benzene (60 ml) was added and the mixture was made alkaline with slow addition of a cold solution of 3.2 g (80 mmol) of sodium hydroxide in 45 ml of water. The organic phase was separated and washed successively with 20 ml portions of  
30 water until the pH < 9 (3-5 times). The organic solution was dried over anhydrous sodium sulphate, treated with charcoal, filtered and evaporated *in vacuum* (t < 45 °C) to give 2.6 g of oil. This residue was dissolved in 5 ml of isopropyl alcohol and acidified (pH 2) with isopropyl alcohol containing dry hydrochloric acid. The product was crystallised from n-hexane to give off-white material.

35 Yield: 2.0 g (38 %)

Mp.: 115-123 °C

Following the process described in the previous example the following compounds were prepared:

*Example 5:*

- 5 **N-[2-hydroxy-3-(1-piperidiny)propoxy]-benzenecarboximidoyl chloride monohydrochloride** (compound No. 5.)

Starting material: N-[2-hydroxy-3-(1-piperidiny)propoxy]-benzenecarboximidamide

Yield: 23 %

Mp.: 140-145 °C

10

*Example 6:*

- N-[2-hydroxy-3-(1-piperidiny)propoxy]-4-pyridinecarboximidoyl chloride (Z)-2-butenedioate (1:1)** (compound No. 6.)

Starting material: N-[2-hydroxy-3-(1-piperidiny)propoxy]-4-pyridinecarboximidamide

- 15 In this case the final product was isolated at the end of the work-up procedure by dissolving the crude base in acetone, and adding an equivalent amount of maleic acid.

Yield: 25 %

Mp.: 150 - 154 °C

- 20 *Example 7:*

- N-[2-hydroxy-3-(1-piperidiny)propoxy]-2-nitrobenzenecarboximidoyl chloride monohydrochloride** (compound No. 7.)

Starting material:

- 25 N-[2-hydroxy-3-(1-piperidiny)propoxy]-2-nitrobenzenecarboximidamide

Yield: 36 %

Mp.: 158-162 °C

*Example 8: Hiba! A könyvjelző nem létezik.*

- 30 **N-(3-(1-piperidiny)propoxy)-3-pyridinecarboximidoyl chloride dihydrochloride** (compound No. 8.)

Starting material: N-[3-(1-piperidiny)propoxy]-3-pyridinecarboximidamide

Yield: 33 %

Mp.: 178-182 °C

35

*Example 9:*

- N-[3-(1-piperidiny)propoxy]-3-nitrobenzenecarboximidoyl chloride**

**monohydrochloride** (compound No. 9.)

Starting material: N-[3-(1-piperidinyl)propoxy]-3-nitrobenzenecarboximidamide

Yield: 49%

Mp.: 173-175 °C

*Example 10:***N-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3-trifluoromethyl-benzamide**  
(compound No. 10.)**Procedure:**

1.3 ml (15.2 mmol) of epichlorohydrin was added to a solution of 1.6 ml (15.2 mmol) of *tert*-butylamine in 8 ml of ethanol during 10 minutes with stirring, keeping the temperature below 20 °C, and allow to stand for 3 days. Separately, 0.8 g (14.3 mmol) of potassium hydroxide was dissolved in a mixture of 20 ml of ethanol and 3 ml of water and into this solution 3.42 g (15.2 mmol) of N-hydroxy-3-(trifluoromethyl)-benzamide potassium salt and the formerly prepared solution of epichlorohydrin and *tert*-butylamine were added. The reaction mixture was stirred and boiled for 10 hours, then the solvent was evaporated. The residue was triturated with 20 ml of dichloromethane and 10 ml of water, the organic phase was separated, washed with 5 ml of water and 5 ml of saturated sodium chloride solution, dried over sodium sulphate, filtered and evaporated. The oily residue was crystallised in a mixture of acetone-hexane to yield white powder as title compound.

Yield: 0.85 g (17.3 %)

Mp.: 156-158 °C

IR (KBr): 2976, 2858, 1612, 1556, 1379, 1352, 1313, 1273, 1165, 1130, 1072, 694 cm<sup>-1</sup>*Example 11:***N-hexyl-N'-[2-hydroxy-3-(1-piperidinyl)propoxy]-urea** (compound No. 11.)**Procedure:**

To the solution of 8.0 g (45.9 mmol) of 1-aminooxy-2-hydroxy-3-(1-piperidinyl)-propane dissolved in 60 ml of chloroform 4.9 ml (45.9 mmol) of hexylisocyanate was added and the reaction mixture was stirred for 20 hours at room temperature. After addition of a further 1.6 ml (15 mmol) of hexylisocyanate, the stirring was continued for two more hours, when the solvent was evaporated *in vacuum*. White crystalline product was obtained by triturating with petroleum ether.

Yield: 9.9 g (72 %)

Mp.: 50-52 °C

IR (KBr): 3310,2932,2858,2804,1666,1551,1454,1377,1306, 1092,1040,995,791,725,  
604 cm<sup>-1</sup>

Following the process described in the previous example the following compounds were  
5 prepared:

*Example 12:*

**N-hexyl-N'-[3-(1-piperidinyl)propoxy]-urea** (compound No. 12.)

Starting material: 1-aminooxy-3-(1-piperidinyl)-propane

10 Yield: 85 % (oil)

IR (KBr): 3354,2932,2856,2810,2777,1666,1543,1486,1377,1308,1155,1134,1076 cm<sup>-1</sup>

*Example 13:*

**5,6-Dihydro-5-(1-piperidinyl)methyl-3-(3-pyridyl)-4H-1,2,4-oxadiazine**

15 **Procedure:**

Step a)

17.5 g (0.05 mole) of N-[2-hydroxy-3-(1-piperidinyl)propoxy]-3-pyridinecarbox-imidamide  
dihydrochloride was dissolved in 50 ml of thionyl chloride, boiled for one hour, then the  
mixture was evaporated to dryness. The residue was dissolved in 300 ml of methanol, treated  
20 with charcoal and after filtration the solvent was evaporated in reduced pressure. The residue  
was dissolved in the minimum amount of ethanol and refrigerated to yield crystalline N-[2-  
chloro-3-(1-piperidinyl)propoxy]-3-pyridinecarboximidamide dihydrochloride as intermediate  
compound.

Yield: 13.2 g (71 %)

25 Mp.: 127-145 °C

Step b)

13.2 g (35.7 mmole) of N-[2-chloro-3-(1-piperidinyl)propoxy]-3-pyridinecarbox-imidamide  
dihydrochloride was added to a solution of 16.5 g (143.5 mmole) of potassium *tert*-butoxide  
dissolved in 150 ml of *tert*-butanol. The mixture was boiled for 6 hours, then evaporated *in*  
30 *vacuum*. 100 ml of 5 % sodium hydroxide solution was added and the mixture was extracted  
three times with 300 ml portions of ethyl acetate. The organic layer was dried over sodium  
sulphate, filtered and evaporated to dryness. The residue was triturated with diethyl ether to  
yield the title compound as white crystals.

Yield: 3.5 g (38 %)

35 Mp.: 157.5-158 °C

*Example 14.: Tablets*

For the production of 200 mg tablets containing 50 mg of effective substance use:

- 50 mg of N-[2-hydroxy-3-(1-piperidinyl)propoxy]-benzenecarboximidoyl chloride  
5 monohydrochloride  
129 mg of microcrystalline cellulose (e.g. "Avicel ph 102")  
20 mg of polyvinyl-pirrolidone (e.g. "Polyplasdone XL")  
1 mg of magnesium stearate

10 *Example 15.: Capsules*

For a 300 mg capsule use:

- 50 mg of N-[2-hydroxy-3-(1-piperidinyl)propoxy]-2-nitro-benzenecarboximidoyl chloride  
monohydrochloride  
10 mg of yellow bee wax  
15 10 mg of soybean oil  
130 mg of vegetable oil  
100 mg of capsule cell

*Example 16.: Solution*

20 For 100 ml solution use:

- 500 mg of N-[2-hydroxy-3-(1-piperidinyl)propoxy]-2-thiophenecarboximidoyl chloride  
monohydrochloride  
10 g of sorbit  
0.05 g of saccharine sodium  
25 ad 100 ml of twice distilled water.

*Example 17: Injection vial*

For each 2 ml injection vial containing 2 mg of effective substance use:

- 2 mg of 5,6-Dihydro-5-(1-piperidinyl)methyl-3-(3-pyridyl)-4H-1,2,4-oxadiazine  
30 ad 2.0 ml of physiological saline solution, pyrogen-free, sterile.

*Example 18: Infusion solution*

For 500 ml of infusion solution use:

- 20 mg of N-hexyl-N'-[3-(1-piperidinyl)propoxy]-urea  
35 ad 500 ml of physiological saline solution, pyrogen-free, sterile.

## CLAIMS

1. Use of the hydroxylamine derivatives of general formulae (I) and (II) - wherein R<sup>1</sup> and R<sup>2</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom in-between form a saturated 5 - 7 membered heterocyclic group, containing optionally further nitrogen and/or oxygen heteroatoms,

A refers to a straight or branched alkyl group of 4 to 12 carbon atoms, a phenyl group, substituted or unsubstituted, containing preferably an alkyl-, haloalkyl- or nitro group as substituent, or a 5 - 6 membered heteroaromatic ring containing nitrogen, oxygen or sulphur, in general formula (I), Z refers to a covalent bond, and in general formula (II) to a covalent bond or a =NH group,

in general formula (I), X refers to a halogen atom or to a -NR<sup>3</sup>R<sup>4</sup> group, wherein R<sup>3</sup> and R<sup>4</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, while in general formula (II) X refers to an oxygen atom,

in general formula (II), R' refers to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, and

in general formulae (I) and (II), Y refers to a hydrogen atom, a hydroxyl group or an acyloxy group, which contains preferably the acyl part of a long chain fatty acid of 8 to 22 carbon atoms, or of a cyclic aromatic carboxylic acid as its acyl component,

and in the compounds of general formula (I) wherein X refers to a -NR<sup>3</sup>R<sup>4</sup> group and Y refers to a hydroxyl group, the X group is condensed with the Y substituent to form the intramolecular ring represented by general formula (III), in which formula A, Z, R<sup>1</sup> and R<sup>2</sup> have the same reference as above,

and the salts and optically active forms of these compounds in the preparation of medicine to be used in the treatment or prevention of illnesses connected with the dysfunction of the endothelial cells.

2. The use of N-[2-benzoyloxy-3-(1-piperidinyl)propoxy]-3-pyridinecarboximidamide (Z)-2-butenedioate (1:1) as active ingredient in the process of claim 1.

3. The use of N-[2-palmitoyloxy-3-(1-piperidinyl)propoxy]-3-pyridinecarboximidamide monohydrochloride as active ingredient in the process of claim 1.

4. The use of N-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3-trifluoromethylbenzenecarboximidoyl chloride monohydrochloride as active ingredient in the process of claim 1.

5. The use of N-[2-hydroxy-3-(1-piperidinyl)propoxy]-2-thiophenecarboximidoyl chloride monohydrochloride as active ingredient in the process of claim 1.



6. The use of N-[2-hydroxy-3-(1-piperidiny)propoxy]-benzenecarboximidoyl chloride monohydrochloride as active ingredient in the process of claim 1.

7. The use of N-[2-hydroxy-3-(1-piperidiny)propoxy]-4-pyridinecarboximidoyl chloride (Z)-2-butenedioate as active ingredient in the process of claim 1.

5 8. The use of N-[2-hydroxy-3-(1-piperidiny)propoxy]-2-nitrobenzenecarboximidoyl chloride monohydrochloride as active ingredient in the process of claim 1.

9. The use of N-[3-(1-piperidiny)propoxy]-3- pyridinecarboximidoyl chloride dihydrochloride as active ingredient in the process of claim 1.

10 10. The use of N-[3-(1-piperidiny)propoxy]-3-nitrobenzenecarboximidoyl chloride monohydrochloride as active ingredient in the process of claim 1.

11. The use of N-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3-trifluoromethyl- benzamide as active ingredient in the process of claim 1.

12. The use of N-hexyl- N'-[2-hydroxy-3-(1-piperidiny)propoxy]-urea as active ingredient in the process of claim 1.

15 13. The use of N-hexyl-N'-[3-(1-piperidiny)propoxy]-urea as active ingredient in the process of claim 1.

14. The use of 5,6-Dihydro-5-(1-piperidiny)methyl-3-(3-pyridyl)-4*H*-1,2,4-oxadiazine as active ingredient in the process of claim 1.

20 15. Method of treatment or prevention of illnesses connected with the dysfunction of the endothelial cells by administering to the patient hydroxylamine derivatives of the general formulae (I) and (II) wherein

R<sup>1</sup> and R<sup>2</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom in-between form a saturated 5 - 7 membered heterocyclic group , containing optionally further nitrogen and/or oxygen  
25 heteroatoms,

A refers to a straight or branched alkyl group of 4 to 12 carbon atoms, a phenyl group, substituted or unsubstituted, containing preferably an alkyl-, haloalkyl- or nitro group as substituent, or a 5 – 6 membered heteroaromatic ring containing nitrogen, oxygen or sulphur, in general formula (I), Z refers to a covalent bond, and in general formula (II) to a covalent  
30 bond or a =NH group,

in general formula (I), X refers to a halogen atom or to a - NR<sup>3</sup>R<sup>4</sup> group, wherein R<sup>3</sup> and R<sup>4</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, while in general formula (II) X refers to an oxygen atom,

in general formula (II), R' refers to a hydrogen atom or a straight or branched alkyl group of 1  
35 to 6 carbon atoms, and

in general formulae (I) and (II), Y refers to a hydrogen atom, a hydroxyl group or an acyloxy group, which contains preferably the acyl part of a long chain fatty acid of 8 to 22 carbon atoms, or of a cyclic aromatic carboxylic acid as its acyl component,

and in the compounds of general formula (I) wherein X refers to a -NR<sup>3</sup>R<sup>4</sup> group and Y refers to a hydroxyl group, the X group is condensed with the Y substituent to form the intramolecular ring represented by general formula (III), in which formula A, Z, R<sup>1</sup> and R<sup>2</sup> have the same reference as above or the salts and optically active forms thereof.

16. Pharmaceutical products for the treatment and prevention of illnesses connected with the dysfunction of the vascular endothelial cells, comprising as active ingredient (apart from the usual carriers and auxiliary substances used in pharmaceutical compositions) 0.5-95.5 m/m% hydroxylamine derivative of general formula (I) or (II), or the salts or optically active forms thereof, wherein

R<sup>1</sup> and R<sup>2</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom in-between form a saturated 5 - 7 membered heterocyclic group, containing optionally further nitrogen and/or oxygen heteroatoms,

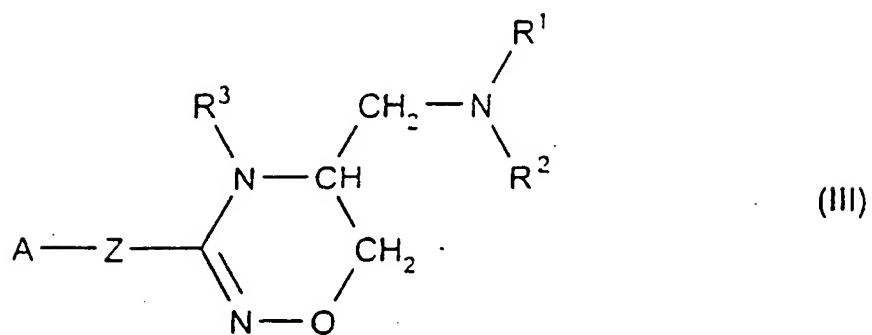
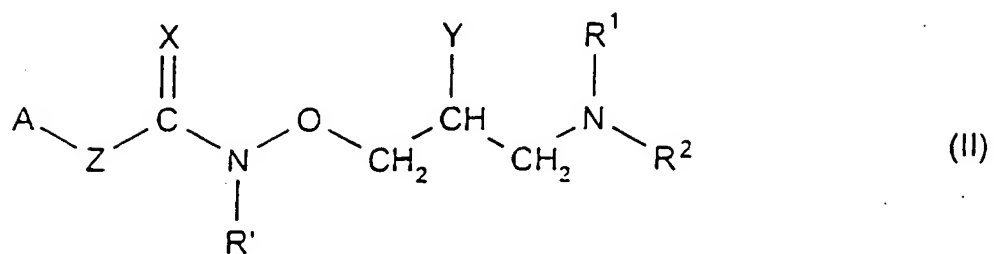
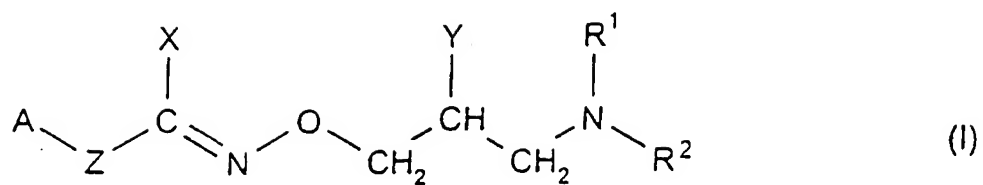
A refers to a straight or branched alkyl group of 4 to 12 carbon atoms, a phenyl group, substituted or unsubstituted, containing preferably an alkyl-, haloalkyl- or nitro group as substituent, or a 5 - 6 membered heteroaromatic ring containing nitrogen, oxygen or sulphur, in general formula (I), Z refers to a covalent bond, and in general formula (II) to a covalent bond or a =NH group,

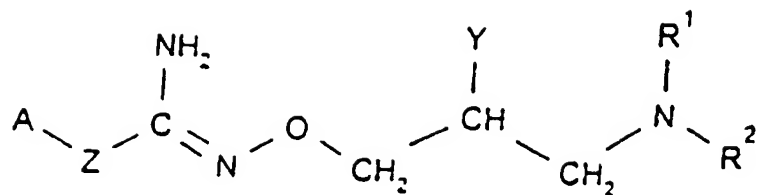
in general formula (I), X refers to a halogen atom or to a -NR<sup>3</sup>R<sup>4</sup> group, wherein R<sup>3</sup> and R<sup>4</sup> independently refer to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, while in general formula (II) X refers to an oxygen atom,

in general formula (II), R' refers to a hydrogen atom or a straight or branched alkyl group of 1 to 6 carbon atoms, and

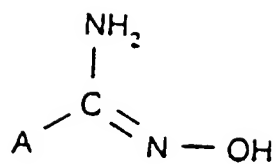
in the general formulae (I) and (II), Y refers to a hydrogen atom, a hydroxyl group or an acyloxy group, which contains preferably the acyl part of a long chain fatty acid of 8 to 22 carbon atoms, or of a cyclic aromatic carboxylic acid as its acyl component,

and in the compounds of general formula (I) wherein X refers to a -NR<sup>3</sup>R<sup>4</sup> group and Y refers to a hydroxyl group, the X group is condensed with the Y substituent and forms the intramolecular ring represented by general formula (III), in which formula A, Z, R<sup>1</sup> and R<sup>2</sup> have the same reference as above.

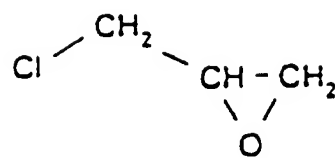




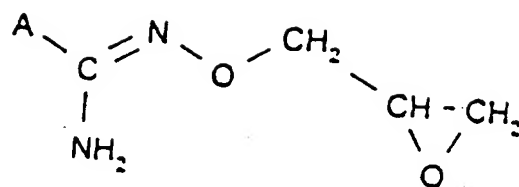
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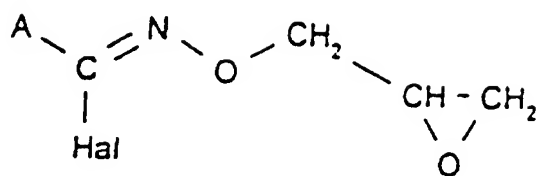
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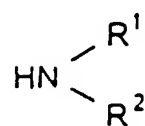
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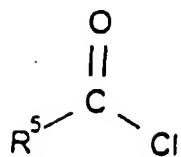
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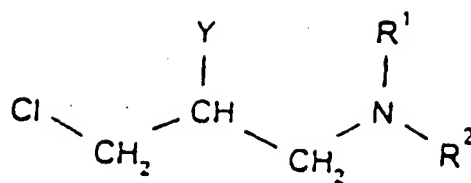
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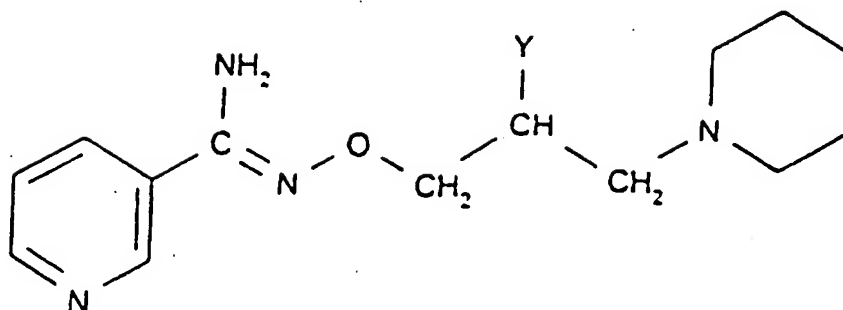
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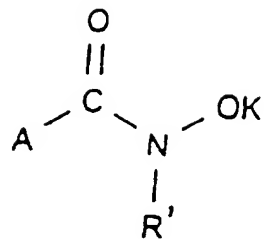
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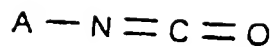
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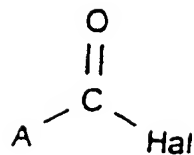
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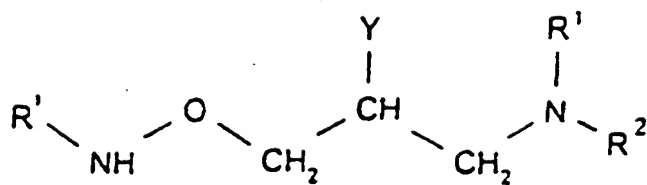
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(XV)



(XVI)



(XIV)